Sudden unexpected death in infants under 3 months of age and vaccination status – a case-control study

Annie-Pierre Jonville-Béra,[1] Elisabeth Autret-Leca,[1] Florence Barbeillon,[1] Josepha Paris-Llado[2] & the French Reference Centers for SIDS

[1]*Department of Clinical Pharmacology and Regional Drug Monitoring Center University Hospital of Tours and* [2]*Unité Inserm U 149 Cochin Port Royal University Hospital, Paris, France*

Aims To determine whether DTPP + Hib vaccination (diphtheria, tetanus, pertussis, poliomyelitis +/− haemophilus) increased the risk of sudden unexpected death (SUD) in children under 3 months of age.

Methods We conducted a multicentre case-control study in the 28 French 'SIDS Centers'. Case selection was based on death labelled sudden infant death syndrome (SIDS) of an infant aged between 30 and 90 days. Three living controls were selected, matched for sex, gestational age and born immediately after the victim in the same maternity unit.

Results We identified 114 cases of SUD aged between 30 and 90 days and 341 live controls matched for age and sex and born in the same maternity unit as the case. DTPP ± Hib immunization did not increase the risk of SUD (OR 1.08) (95% CI 0.49, 2.36) in children under 3 months of age when adjusted for sleeping position, illness in the week before death, maternal tobacco consumption, birth weight, type of mattress, breastfeeding and sex. However, low birth-weight (6.53 [2.29, 18.9]), multiple birth (5.1 [1.76, 15.13]), no breastfeeding (1.77 [1.1, 2.85]), prone sleeping position (9.8 [5, 8, 18, 9]), soft mattress (3.26 [1.69, 6.29]), recent illness (3.44 [1.84, 6.41]) and parental smoking (1.74 [1.2, 2.96]) were confirmed as risk factors in early SIDS.

Conclusions DTPP ± Hib immunization is not a risk factor for early SUD. In this population, we found the same risk factors as described for SIDS.

Keywords: aetiology, case-control study, sudden unexpected death, vaccination status

Introduction

Sudden infant death syndrome (SIDS) remains the leading cause of postneonatal death in the first year of life. Among the many hypotheses suggested, research on its aetiology has focused on diphtheria, tetanus and pertussis (DPT) vaccination. Four cases of SIDS following such vaccination were reported in March 1979 in Tennessee, USA [1] and five cases in March 1986 in France [2]. Similarly, from 1986 to 1996, 107 claims concerning early death and pertussis vaccine were referred by the US population to the National Vaccine Injury Compensation Program [3]. Several studies were then conducted to evaluate the relationship between vaccination and SIDS because infants are routinely vaccinated during the period of highest incidence of SIDS. No relationship was found in the majority of studies [1, 4–11]. We carried out a case-control study in France in 1989 in which SIDS was not associated with vaccination, except in early SIDS cases (less than 3 months of age) who were significantly more often vaccinated than the controls [12]. Because the recommended vaccination schedule was modified by the Ministry of Health to a decrease in age for the first DTPP + Hib injection, i.e. 2 months of age instead of 3 months, at the same time as the analysis of the results of our study, our results needed to be confirmed or disproved.

We therefore carried out a prospective case-control study on the vaccination status of early SIDS (i.e. infants

Correspondence: Dr A.-P. Jonville-Béra, Department of Clinical Pharmacology, CRHU de Tours, 2 boulevard Tonnellé, F37044 Tours Cedex, France. Tel.: 33 2 47 47 80 29; Fax: 33 2 47 47 38 26; E-mail: jonville-bera@chu-tours.fr

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who died between 1 and 3 months of age) to assess whether such vaccination increased the risk of SIDS in this population.

Methods

Population

We defined SIDS as the sudden death of any infant or young child which is unexpected by history and in whom a thorough post mortem examination fails to demonstrate an adequate cause of death, and we defined sudden unexpected death (SUD) as the sudden death of any infant in good health until death for whom investigations failed to show an adequate explanation of death but without post mortem examination. Twenty-eight paediatric units located in each Regional University Hospital in France, called 'SIDS Centres', are approved to receive infant victims of SIDS. From February 1995, these 28 SIDS Centres (SC) reported to us all SIDS and SUD occurring in infants between 30 and 90 days of age with a gestational age over 34 weeks and for which parents were interviewed during a consultation within 3 months of death. Three controls were selected per case, matched for sex, age and maternity unit of birth. For each case we identified the first 10 infants born immediately after the index case in the same maternity unit (because child care practice taught to mothers is probably different according to maternity unit) with gestational age of over 34 weeks and matched for sex. Authorization was requested from the parents of the 10 possible controls to give their telephone number for interview in a letter from the Director of the maternity unit. We asked the first three parents who gave consent to reply to a questionnaire during a telephone interview.

Data collection

The standardized questionnaire for cases and controls included sociodemographic data, the medical history of the infant and perinatal factors. Information concerning all vaccines (type and date of administration) received from birth was obtained from the Health and Development Record.

The paediatrician of the SC collected data concerning cases during the consultations following death and we collected data from controls during the telephone interviews.

Size of the sample

The case-control study was designed to have 80% power at a 5% level of significance to detect a twofold increased risk of SIDS, with three controls per case, and for a prevalence of DTPP ± Hib immunization of 13% (observed in our first study [12]). Therefore 136 cases were required.

Main outcome measures

The main criterion was the vaccination status, i.e. whether the child was or was not vaccinated. A case was defined as vaccinated if s/he had been exposed to at least one dose of DT ± pertussis, poliomyelitis or haemophilus vaccine at death and a control was defined as vaccinated if s/he had received at least one dose of DT ± pertussis, poliomyelitis or haemophilus vaccine at the age the matching case died (index day).

In order to eliminate confounding factors, we also compared birth weight, multiple birth, prematurity, breast or bottle feeding, sleeping position, type of mattress, illnesses and drug ingestion in the week before death or the index day, maternal age, parental smoking, family history of SIDS and other vaccines received from birth.

The proportion of SIDS cases seen at the SC was evaluated the year before the study by comparing the number of SIDS victims aged between 30 and 90 days identified by death certificates and the number of sudden infant deaths referred to the SC in the same region.

Quality assessment in nine randomly selected SC (33%) checked whether all the cases of SIDS seen in consultation during the study period and meeting the inclusion criteria had been reported to us.

Data analysis

The Mantel-Haenszel χ^2 test was used for categorical variables and variance analysis was used for continuous variables. A multivariate analysis was carried out using a conditional logistic regression model (included illness in the week before death, maternal tobacco consumption, birth weight, sleeping position, use of a firm mattress, breastfeeding and sex) to estimate the odds ratio of SIDS due to DTPP ± Hib vaccination.

The study was approved by the 'Commission Nationale Informatique et Liberté'.

Results

During the 27 months of the study (February 1995 to March 1997), 114 cases and 341 controls were included (3 controls for 113 cases and 2 controls for 1 case). The study was stopped earlier than planned because of a financial problem related to slowness of inclusion, explained by the decrease in the incidence of SIDS. The proportion of cases seen at the SC was estimated to be between 22% to 100% in the various regions. In the nine randomly selected SC, the quality assessment identified three cases not reported to us of the 16 who met the study criteria.

The median age of cases was 61.5 days (range 30–89 d) and the sex ratio was 1.59 (male/female). Death occurred at the parental home for 95 (83%) cases, and for 88 of these (80%) the usual sleeping position had not changed since birth. The usual sleeping position of cases was 44% prone, 18% supine, 31% lateral and 8% variable. At death 72% had a prone, 14% a supine and 11% a lateral sleeping position. An autopsy was performed in 90 (79%) cases, which we defined as SIDS. The other 24 cases, without autopsy were defined as SUD. The median interval between death and the parents' interview was 8.5 days and for 29% (31/106) the interview took place on the day of death. Parents of the 341 controls were interviewed by telephone, with a median interval of 110 days after the death of the matched case.

Comparison between cases and controls

Maternal age (mean ± s.e. mean) (28 years ± 4.5 *vs* 29 years ± 4.5; $P<0.02$) and infant birth weight (3136 g ± 534 *vs* 3368 g ± 482; $P<0.0001$) were lower for cases than for controls. Cases were more often multiple births than controls, were more often bottle fed at birth, had a prone sleeping position, a recent illness and did not have a firm mattress and were exposed to parental smoking (Table 1). Frequency of DTPP ± Hib immunization was not different between cases and controls (12% *vs* 14%) (Table 2) and thus DTPP ± Hib immunization did not increase the risk of SIDS (OR 1.08 95% CI 0.49, 2.36), even after adjustment for sleeping position, illness in the week before death, maternal tobacco consumption, birth weight, type of mattress, breastfeeding and sex (Table 3). The age at first injection of DTPP ± Hib vaccine was 61 days ± 7.9 for cases and 63 days ± 11.6 for controls ($P=0.62$). The median interval between immunization and death was 16 days (range 3–26 days).

Discussion

Previous studies conducted to evaluate the relationship between DTP vaccination and sudden infant death syndrome (SIDS) were negative, but none was conducted in early SIDS. Our hypothesis was that vaccination induces immunological changes and fever several days later, which can add to other risk factors for SIDS induced by a change in the mother's child care habits because of the immunization, e.g. a heated bedroom, overwrapping and prone sleeping position because of neonatal buttock pain. Moreover, vaccination could be a risk factor varying with age at death, as suggested for maternal smoking [13]. We used a wide definition of SIDS because immunization can perhaps trigger death in infants with other contributory factors (for which other factors may have contributed to unexpected death).

The characteristics of the 114 cases were those usually reported in the literature. The usual risk factors (confounding factors) for SIDS were found in our study: low birth weight [14], low maternal age [15], maternal smoking [16] and prone sleeping position [17]. Prematurity [18] was not found, probably because only children born at more than 34 weeks' gestational age were included. As in previous studies [19], maternal smoking was found to show a dose–response pattern. Other identified risk factors have already been discussed: multiple birth [20], family history of SIDS [21], illness a few days before death [22] and bottle feeding [19]. Use of a soft mattress has not previously been described as a risk factor,

Table 1 Comparison of variables related to neonatal, post natal and parental risk factors between SIDS and controls.

	Proportion (%) of:		*Univariate odds ratio*
	Cases	*Controls*	*(95% CI)*
Multiple birth	11/114 (10)	7/341 (2)	5.10 (1.76–15.13)
Prematurity (34–36 weeks)	9/114 (8)	11/341 (3)	2.57 (0.94–6.96)
Bottle feeding at birth	74/111 (67)	181/341 (53)	1.77 (1.10–2.85)
Usual prone sleeping position	50/114 (44)	31/341 (9)	7.81 (4.49–13.64)
Firm mattress	64/97 (66)	300/341 (88)	0.27 (0.15–0.47)
Recent illness (last 8 days)	45/114 (39)	62/341 (18)	2.93 (1.79–4.82)
Recent medication given (last 8 day)	35/112 (31)	73/336 (22)	1.64 (0.98–2.72)
Maternal smoking (cigarettes/day)			
1–10	18/99 (19)	57/340 (17)	1.33 (0.69–2.55)
11–20	14/99 (15)	41/340 (12)	1.44 (0.69–2.98)
>20	7/99 (7)	4/340 (1)	7.38 (1.83–31.63)
Both parents smokers	32/93 (34)	76/328 (23)	1.74 (1.02–2.96)
Family history of SIDS	11/114 (10)	21/341 (6)	1.63 (0.70–3.71)

Table 2 Comparison of variables related to vaccination between SIDS and controls.

	Proportion (%) of:		*Univariate Odds ratio (95% CI)*
	Cases	*Controls*	
DTPP ± Hib immunization at death or at index day	14/114 (12)	47/341 (14)	0.87* (0.43–1.68)
Type of vaccine received			
DTPP + Hib	13 (93)	42 (90)†	
DTPP	0	4 (8)	
DT + Polio	1 (7)	1 (2)	
Other vaccine received			
BCG vaccine	6/37 (97)	117/123 (95)	1.85 (0.21–42.76)
Hepatitis B vaccine	3/114 (3)	10/341 (3)	0.89 (0.19–3.64)

*Mantel-Haenszel matched Odds ratio and exact 95% Mid-P limits. †$P = 0.36$.

Table 3 Relative risk of SIDS associated with DTPP ± Hib immunization and with other factors.

	Proportion (%) of:		*Multivariate analysis Odds ratio (95% CI)*
	Cases	*Controls*	
DTPP ± Hib immunization			
no	100/114 (88)	294/341 (86)	1
yes	14/114 (12)	47/341 (14)	1.08 (0.49, 2.36)
Usual sleeping position			
side or back	64/114 (56)	310/341 (91)	1
prone	50/114 (44)	31/341 (9)	9.8 (5.8, 9.9, 18)
Birth weight			
≥2500 g	98/113 (87)	333/341 (98)	1
<2500 g	15/113 (13)	8/341 (2)	6.53 (2.29, 18.9)
Illness the week before death			
no	69/114 (61)	279/341 (82)	1
yes	45/114 (39)	62/341 (18)	3.44 (1.84, 6.41)
Type of mattress			
firm	64/97 (66)	300/341 (88)	1
not firm	33/97 (34)	41/341 (12)	3.26 (1.69, 6.29)
Maternal tobacco consumption			
no	55/99 (56)	232/340 (68)	1
yes	44/99 (44)	108/340 (32)	1.72 (0.95, 3.11)
Sex			
male	70/114 (61)	210/341 (62)	1
female	44/114 (39)	131/341 (38)	1.16 (0.64–2.11)
Breastfed at birth			
no	74/111 (67)	181/341 (53)	1
yes	37/111 (33)	160/341 (47)	0.55 (0.3–1)

but Brooke [23] found an increased risk for infants who slept on an old mattress.

DTPP ± Hib vaccination does not constitute a risk factor for early SIDS and the odds ratio did not vary when it was adjusted for the risk factors found in this study (OR 1.08 95% CI 0.49, 2.36). Thus, we reasonably exclude the hypothesis of a two-fold increase in risk. The power of the study (74%) is near the 80% required and confirms that if the risk exists it is probably less than 2, the value used in the calculation of the number of subjects. As we stopped the study before including the 136 cases required, we made the hypothesis of maximum bias (all new cases included being immunized and none of their controls) for calculation of the odds ratio. Even in this situation the OR remained 1.

Moreover, when we analysed separately the 24 cases who did not have an autopsy, because they were perhaps different from the others and were not strictly definable as SIDS, the OR for DTPP ± Hib vaccination was 0.42 [0.06, 1.8] ($P < 0.42$). This result is not statistically significant, but it suggests that immunization might decrease the risk of death in this subgroup. In fact, the

SUD cases were probably in poorer health than the SIDS cases and therefore were less often immunized.

As in all case-control studies, several biases in our study might explain a failure to demonstrate a risk related to vaccination. A selection bias affecting the representativeness of the cases notified cannot be excluded. The cases referred to the SC represented the majority of deaths from SIDS and the exhaustivity of collection of cases reported is probably underestimated because death certificates are not completed very accurately and the diagnosis of SIDS might have been attributed without being confirmed. Several cases were not included because the parents did not attend the SC for consultation during the 3 months following the deaths of their children. If these parents were more often of low social economic status, the percentage of immunized cases may have been overestimated, because the sociodemographic risk factors for SIDS are similar to those for not being immunized [24]. Control selection from the same hospital as the index case reduced the bias caused by post natal ward education but could conceivably have introduced a selection bias which would act to remove case-control differences on factors related to socio-economic factors.

Finally, parents with no telephone or who were slower to give consent were perhaps of lower socio-economic status and their infants might not have been vaccinated. In this case the vaccination rate for controls might have been overestimated and have hidden an increased risk of SIDS related to vaccination.

The only difference found between vaccinated and nonvaccinated controls was that vaccinated controls more frequently slept in a prone position than nonvaccinated controls (19% *vs* 7%; $P<0.02$). However, this is not a confounding factor because the lack of association persisted after adjustment for this variable (OR = 0.77; 95% CI 0.35, 1.58). Moreover, this confounding factor increased the risk related to vaccination and this variable was taken into account in the logistic regression. The interval before interviewing parents of controls, explained by the procedure of identification and selection of the controls, could have produced some recall bias for some variables except for vaccination, because information concerning type and date of vaccination was obtained from the child's Health and Development Record.

As for older SIDS cases, DTPP ± Hib vaccination does not constitute a risk factor for early SIDS, even in infants vaccinated before 3 months of age. Moreover, recent epidemiological evidence indicates that infants immunized against DTP are perhaps at decreased risk of SIDS (25, 26).

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